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November 27, 2001

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Attention: TSCA Section 8(e)
U.S. Environmental Protection Agency
ICC Building
1200 Pennsylvania Avenue, NW
Washington, DC 20460



BEHQ-91-1347

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Dear 8(e) Coordinator:

8EHQ-0991-1347

Referencing my letters to you of September 6, 2001 and November 7, 2001 on this subject, following are results from the terminal synopsis of the 90-day (13 week) subchronic oral (feeding) study initiated on August 6, 2001 on the referenced chemical. These results have just become available following analysis, including statistical evaluation, of all the collected clinical data. The test was run in accordance with OECD Protocol 408. The in-life phase of the study was completed on November 5, 2001.

Groups of 10 male and 10 female Crl:CD(SD) IGS BR rats per dose group were administered the test compound through the diet. Test concentrations were 0, 10, 50 and 150 mg/kg body weight/day. In-life phase evaluations included clinical observations, detailed physical examinations, sensory reactivity and grip strength, motor activity, body weight changes, food and water consumption and ophthalmic, hematologic and biochemical examinations.

The mortality findings (5 unscheduled deaths) have been reported earlier. Based on analysis of the results it is uncertain at this stage whether these deaths were treatment related.

Besides the clinical signs reported earlier elevated abnormal gait was noted in one female receiving 150 mg/kg/day and one female receiving 50 mg/kg/day during the eighth week of treatment. Besides this and the earlier reported findings no other clinical signs attributable to treatment were observed.

Group mean body weight gain for animals receiving 150 mg/kg/day was significantly reduced when compared to concurrent controls. Slightly reduced group mean body weight gain was noted for groups receiving 50 mg/kg/day. A dosage-related trend was apparent for both males and females. Group mean body weight gain for groups receiving 10 mg/kg/day was comparable to the controls.



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Significantly lower group mean food consumption was noted for males receiving 50 or 150 mg/kg/day and slightly lower food consumption was noted for females receiving 150 mg/kg/day. The effect in males was apparent from the commencement of treatment; that for females receiving 150 mg/kg/day was mainly due to the effect during the first week when 4 females were sacrificed due to poor condition.

Animals receiving 150 mg/kg/day demonstrated inferior food conversion efficiency compared to concurrent controls. The effect in females was mainly attributed to the effects seen during the first week. Food conversion efficiency for animals receiving 10 or 50 mg/kg/day was essentially similar to that of the controls. Since food consumption and food efficiency ratios may well have been impacted by the substantially lower food intake of the decedent animals during the first week of the test, the toxicological significance of this observation is questionable.

The results of neurological screening (primarily functional observation battery) conducted during the course of the in-life phase, are currently being reviewed. Preliminary results reveal lower activity in females dosed 150 mg/kg/day.

Investigation of hematological parameters in Week 13 revealed lower group mean hemoglobin concentrations (Hb), mean corpuscular hemoglobin (MCH) and mean corpuscular volume (MCV) for most treated groups. The effect in males and females receiving 150 mg/kg/day was statistically significant. Lower group mean hematocrit (Hct) for males receiving 150 mg/kg/day, Hb for females receiving 50 or 10 mg/kg/day, mean corpuscular hemoglobin concentrations (MCHC) for females receiving 150 or 50 mg/kg/day and MCH for males and females receiving 50 mg/kg/day were observed and these differences achieved statistical significance versus controls. A dosage-related trend was apparent for many of these parameters though the individual values showed some degree of overlap with the controls. Statistically significant shorter group mean activated partial thromboplastin time (APPT) was noted in males receiving 150 mg/kg/day. A statistically significant increased group mean platelet value was noted for males receiving 150 mg/kg/day. The toxicological significance of these findings is presently uncertain.

Investigation of biochemical parameters in Week 13 revealed lower group mean aspartate amino-transferase (AST) for male groups receiving 50 or 150 mg/kg/day in comparison with the controls. Statistically significant higher group mean urea values were noted for males and females receiving 150 mg/kg/day in comparison with the controls. Significantly lower group mean potassium values were noted for all female groups and a significantly lower group mean sodium value was noted for males receiving 150 mg/kg/day. Statistically significant lower group mean total cholesterol values were noted in females receiving 50 or 150 mg/kg/day. Statistically significant lower group mean albumin values were noted for all treated male groups. The toxicological significance of these findings is presently uncertain.

Analysis of terminal organ weight data revealed statistically significant higher group mean adrenal weights for females receiving 50 or 150 mg/kg/day and higher testes weights for males receiving the same dosages. There was no dose-related trend in the females. All other group mean values were generally similar to those of concurrent controls.

Macroscopic examinations performed at termination revealed distension of the ileum and jejunum in a greater number of rats treated with 50 or 150 mg/kg/day compared to none in the controls. Examinations also revealed an irregular appearance of the limiting ridge of the stomach in 6/9 male and

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5/6 female rats treated with 150 mg/kg/day and 1/10 male and 6/10 female rats treated with 50 mg/kg/day compared with 0/10 male and female control rats. Roughening of the epithelial aspect of the forestomach was seen in 3/9 male rats treated with 150 mg/kg/day and 2/10 male rats treated with 50 mg/kg/day compared with 0/10 male control rats. The incidence and distribution of all other macroscopic findings were considered to fall within the expected background range of macroscopic changes. The significance of these findings will be reviewed after microscopic pathology is completed.

EPA is being notified of these findings under TSCA §8(e) because they are believed to be reportable based on guidance provided in the Agency's June 1991 TSCA Section 8(e) Reporting Guide.

You may contact me on 856/540-4576 if there are any questions.

Yours truly,



Kavsy D. Dastur
Manager, Product Toxicology & Chemical
Regulations

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US certified mail

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